Marked-up copies of the original text of the amended specification are attached to this amendment. Material inserted is indicated by underline (underline) and material deleted is indicated by angled brackets (<angled brackets>).

Clean copy of the amended specification (paragraph on page 14 at line 26-page 15 at line 11)

To increase the number of permutations in an adapter library, two separate oligonucleotide libraries may be generated, one with single stranded oligonucleotides with regions that will correspond to the single stranded region of the first nucleic acid molecule fragment and the second library with single stranded oligonucleotides with regions that will correspond to the single stranded region of the second nucleic acid molecule (e.g. vector). However in common in each member of the library is a complementary region, such that when one member from the first library is selected and combined with a member of the second library, they will hybridize leaving free the relevant single stranded regions. Thus for example to generate an adapter with an AA overhang and a TC overhang to bind to the first and second nucleic acid molecules respectively, members of the different libraries such as GGCCCCCNNAA[SEQ ID NO:1]may be combined with 3'-TCNNNCCGGGG-5'[SEQ ID NO:2] to form:

GGCCCCCNNAA[SEQ ID NO:1]
TCNNNCCGGGG[SEQ ID NO:2]

which exhibits the appropriate overhangs. When using only two 16 member libraries this allows the production of 256 different adapters.

Clean copy of the amended specification (paragraph on page 16 at line 20-page 17 at line 11)

Over 100 classes of IIS restriction endonucleases have been identified and there are large variations both with respect to substrate specificity and cleaving pattern. In addition, these enzymes have proved to be well suited to "module swapping" experiments so that one can create new enzymes for particular requirements (Huang-B, et al.; J-Protein-Chem. 1996, 15(5):481-9, Bickle, T.A.; 1993 in Nucleases (2nd edn), Kim-YG et al.;PNAS 1994, 91:883-887). In these experiments the binding domain of transcription factor *Sp*1 was merged with the cleavage domain of *Fok*I to construct a class IIS restriction endonuclease that makes a 4-base overhang with *Sp*1 sites. In other experiments a class IIS restriction endonuclease that cuts outside the binding sites of transcription factor Ultrabithorax was generated. Corresponding experiments have been conducted on class I enzymes. By merging the N-terminal part of the *hsdS* sub-unit of *Sty*R 1241 (which recognizes $GAAN_6RTCG$[SEQ ID NO:82]) with the C-terminal part of the *hsdS* sub-unit of *Sty*R 1241 (which recognizes $TCAN_7RTTC$[SEQ ID NO:83]) a new enzyme that recognizes the sequence $GAAN_6RTTC$[SEQ ID NO:84] was constructed. Several other experiments have been carried out with similar success. Unlike in the case of ordinary class II enzymes, it is therefore reasonable to assume that a number of new IIS and IP restriction enzymes can be constructed and adapted to cloning requirements that may arise in the future. Very many combinations and variants of these enzymes can therefore be used according to the principles described herein.

Clean copy of the amended specification (paragraph on page 44 at line 30-page 45 at line 25)

The following examples are given by way of illustration only in which the Figures referred to are as follows:

Figure 1 shows a schematic representation of how the method of the invention may be used to introduce an insert into a vector, in which the insert is cleaved from the first nucleic acid molecule, associated with adapters and ligated thereto and then ligated into the vector;

Figure 2 shows the production of a fragment chain using 8 "O" and "1" starting fragments with different overhangs (aaaaaaaaaa[SEQ ID NO:100], aaaaaaaaac[SEQ ID NO:54], aaaaaaaccg[SEQ ID NO:57], ccccccccccgg[SEQ ID NO:59], cccccccccgcg[SEQ ID NO:56], ccccccccctttt[SEQ ID NO:53], gggggggggaaa[SEQ ID NO:51], ggggggggaac[SEQ ID NO:52], ggggggggccg[SEQ ID NO:55], ttttttttcgg[SEQ ID NO:60], ttttttttgcg[SEQ ID NO:58], ttttttttttt[SEQ ID NO:101]);

Figure 3 shows the production of a 64 fragment chain in which 8 chains are produced comprising 8 fragments each, in which the termini of chains 1 and 2, and 2 and 3 etc. are complementary such that they may be ligated together (aaaaaaaaaa[SEQ ID NO:100], aaaaaaaaaaaaa[SEQ ID NO:102], aaagggggggggaaa[SEQ ID NO:61], aacaaaaaaaaaa[SEQ ID NO:62], aacgggggggggaaa[SEQ ID NO:103], cttccccccccccg[SEQ ID NO:104], ctttttttttttcg[SEQ ID NO:105], ggggggggaaa[SEQ ID NO:51], gttccccccccccg[SEQ ID NO:65], gttttttttttcg[SEQ ID NO:66], tttccccccccccg[SEQ ID NO:63], ttttttttttttcg[SEQ ID NO:64]);

Figure 4 shows 3 techniques for mixing "O", "1" fragments from a library of fragments ordered for each position, in which in A)

appropriate fragments are selected by aspiration from appropriate wells, B) appropriate fragments are released from the library is wells and C) a flow cytometer is used to direct appropriate droplets to the mixing chamber;

Figure 5 shows PCR amplification of signal chain 1-0-1-0-0 using SP6 and T7 primers. Lane 1: 1 µg of 1 kb DNA ladder (Gibco BRL), Lane 2: 10 µl of PCR amplified fragment chain DNA using SP6 and T7 primers. Lane 3: Same as lane 2 except for the use of SP6 and T7-Cy5 primers; and

Figure 6 shows the use of primer pairs during the process of amplification to join together fragment chains.

Clean copy of the amended specification (paragraph on page 48 at lines 21-34)

Materials:

Oligonucleotides used to address *Phi*X174 overhangs:

BbvI overhang 1a:

5'- CGA GCG CCT CCA GTG CAG CGG AG[SEQ ID NO:3]

BbvI overhang 5a:

5'- TATC GCG CCT CCA GTG CAG CGG AG[SEQ ID NO:4]

BbvI overhang 6b:

5'- CTCT GCG CCT CCA GTG CAG CGG AG[SEQ ID NO:5]

BbvI overhang 6(delC):

5'- CTCT CTC CGC TGC ACT GGA GGC GC[SEQ ID NO:6]

BbvI overhang 7a:

5'- CAAC GCG CCT CCA GTG CAG CGG AG[SEQ ID NO:7]

BbvI overhang 9b:

5'- GGTA GCG CCT CCA GTG CAG CGG AG[SEQ ID NO:8]

Clean copy of the amended specification (paragraph on page 49 at lines 1-5)

Oligonucleotides used to address pUC19 overhangs:

Cloning site 1a

5'- AAGAG CTC CGC TGC ACT GGA GGC GC[SEQ ID NO:9]

Cloning site 1b

5'- CTCTT CTC CGC TGC ACT GGA GGC GC[SEQ ID NO:10]

Clean copy of the amended specification (paragraph on page 53 at line 11-page 54 at line 6)

In this Example, the location of the binding motifs of the initiation linkers is shown below:

*Fok*I	----------GGATG----
*Bst*71I	--GCAGC----------
*Hga*I	----------GACGC
*Bpl*I	----------GAG-----CTC----------
*Bae*I	---------CYATG----CA----------
*Cje*I	----------CCA------GT---------
*Hae*IV	-------GAY-----RTC----------
Consensus	--GCAGCGACCATGAGTCCA-CTC--GTGGATGACGC[SEQ ID NO:11]

Initiation linkers:

X=0: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGPPPPPP[SEQ ID NO:12]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTAC[SEQ ID NO:69]

X=1: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATG-PPPPPP[SEQ ID NO:13]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTAC-[SEQ ID NO:70]

X=2: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATG--PPPPPP[SEQ ID NO:14]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTAC--[SEQ ID NO:71]

X=3: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATG---PPPPPP[SEQ ID NO:15]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTAC---[SEQ ID NO:72]

X=4: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGACGCPPPPPP[SEQ ID NO:16]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTACTGCG[SEQ ID NO:73]

X=5: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGACGC-PPPPPP[SEQ ID NO:17]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTACTGCG-[SEQ ID NO:74]

X=6: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGACGC--PPPPPP[SEQ ID NO:18]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTACTGCG--[SEQ ID NO:75]

X=7: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGACGC---PPPPPP[SEQ ID NO:19]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTACTGCG---[SEQ ID NO:76]

X=8: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGACGC----PPPPPP[SEQ ID NO:20]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTACTGCG----[SEQ ID NO:77]

X=9: 5' --GCAGCGACCATGAGTCCA-CTC--GTGGATGACGC-----PPPPPP[SEQ ID NO:21]

3' --CGTCGCTGGTACTCAGGT-GAG--CACCTACTGCG-----[SEQ ID NO:78]

Clean copy of the amended specification (paragraph on page 54 at lines 21-35)

Propagation linkers:

FokI: 5'----------GGATG

3'----------CCTACNNNN

Bst71I: 5'----------GCAGC

3'----------CGTCGNNNN

HgaI: 5'----------GACGC

3'----------CTGCGNNNNN[SEQ ID NO:79]

```
SplI:     5'------------GAG-----CTCNNNNN
          3'------------CTC-----GAG
BaeI:     5'------------CCATG----CANNNNN
          3'------------GGTAC----GT
HaeIV:    5'------------GAC-----GTCNNNNNN
          3'------------CTG-----CTG
CjeI:     5'------------CCA------GTNNNNNN
          3'------------GGT------CA
```

Clean copy of the amended specification (paragraph on page 55 at lines 28-36)

The 3'-GAGTGC overhang is then ligated with the X=3 initiation linker and the GTGAA-3' overhang is ligated with the CACTT-3' overhang on the target DNA molecule:

```
5'--GCAGCGACCATGAGTCCA-CTC--GTGGATG---PPPPPP[SEQ ID NO:15]
3'--CGTCGCTGGTACTCAGGT-GAG--CACCTAC---QQQQQQ[SEQ ID NO:85]
------------------GTGAA------------3'
------------------CACTT------------5'
```

Clean copy of the amended specification (paragraphs on page 56 at line 15-page 58 at line 7)

Method 1

Two IIS enzymes that generate 5'-4 base overhangs (*Bbs*I and *Esp*3I):

```
5'..VVVVVVVVGAGC-GAGACG------GAAGAC--GAGCIIIIIIIIII  3'[SEQ ID
NO:86]
```

3' VVVVVVVVCTCG-CTCTGC------CTTCTG--CTCGIIIIIIIIII..5'[SEQ ID NO:87]

After cleavage with *Bbs*I and *Esp*3I:

..VVVVVVVV + GAGC-GAGACG------GAAGAC--[SEQ ID NO:88] +
VVVVVVVVCTCG -CTCTGC------CTTCTG--CTCG[SEQ ID NO:89]

GAGCIIIIIIIIII
IIIIIIIII..

After ligation with T4 DNA ligase:

GAGC-GAGACG------GAAGAC--[SEQ ID NO:88] +
-CTCTGC------CTTCTG--CTCG[SEQ ID NO:89]

..VVVVVVVVGAGCIIIIIIIIII[SEQ ID NO:90]
VVVVVVVVCTCGIIIIIIIIII..[SEQ ID NO:91]

Method 2

One IIS enzyme that generates two 3' 3 base overhangs(*Bsa*XI):

5'..VVVVVVVVGAG---------AC-----CTCC-------GAGIIIIIIIII 3'[SEQ ID NO:92]
3' VVVVVVVVCTC---------TG-----GAGG-------CTCIIIIIIIII..5'[SEQ ID NO:93]

After cleavage with *Bsa*XI:

..VVVVVVVVGAG + ---------AC-----CTCC-------GAG[SEQ ID NO:94]
VVVVVVVV CTC---------TG-----GAGG-------[SEQ ID NO:95]

```
+       IIIIIIIIII
     CTCIIIIIIIIII..
```

After ligation with T4 DNA ligase:

```
   ---------AC-----CTCC-------GAG[SEQ ID NO:94]      +
CTC---------TG-----GAGG-------[SEQ ID NO:95]

..VVVVVVVVGAGIIIIIIIII
  VVVVVVVVCTCIIIIIIIII..
```

Method 3

One IIS enzyme that generates blunt ends (*Mly*I):

```
5'..VVVVVVVV----------------GAGTC-----IIIIIIIII  3'[SEQ ID
NO:96]
3'  VVVVVVVV-----CTGAG----------------IIIIIIIII..5'[SEQ ID
NO:96]
```

After cleavage with *Mly*I:

```
..VVVVVVVV   +   ----------------GAGTC-----[SEQ ID NO:97]  +
  VVVVVVVV       -----CTGAG----------------[SEQ ID NO:97]

IIIIIIIII
IIIIIIIII..
```

After ligation with T4 DNA ligase:

```
----------------GAGTC-----[SEQ ID NO:97]                  +
-----CTGAG----------------[SEQ ID NO:97]
```

..VVVVVVVVIIIIIIIIII
VVVVVVVVIIIIIIIIII..

Clean copy of the amended specification (paragraph on page 71 at line 14-page 72 at line 4)

Based upon the overhang pairs, a set of five library components was made by annealing complementary oligonucleotides in separate tubes:
signal 1:
5'-TAATACGACTCACTATACCACAAGTTTGTACAAAAAAGCAGGCTCTATTC-3'[SEQ ID NO:22]
and
5'-TAGGAAGAATAGAGCCTGCTTTTTTGTACAAACTTGTGGTATAGTGAGTCGTATTA-3' [SEQ ID NO:23];
signal 2:
5'-TTCCTATGCAGTGGACCACTTTGTACAAGAAAGCTGGGTTGCAGT-3'[SEQ ID NO:24] and 5'-GCAACTACTGCAACCCAGCTTTCTTGTACAAAGTGGTCCACTGCA-3'[SEQ ID NO:25];
signal 3:
5'-AGTTGCTTGACGCCACAAGTTTGTACAAAAAAGCAGGCTTTGACG-3'[SEQ ID NO:26] and 5'-CGACATCGTCAAAGCCTGCTTTTTTGTACAAACTTGTGGCGTCAA-3'[SEQ ID NO:27];
signal 4:
5'-ATGTCGAAGGGCGGACCACTTTGTACAAGAAAGCTGGGTAAGGGC-3'[SEQ ID NO:28] and 5'-GACAGGGCCCTTACCCAGCTTTCTTGTACAAAGTGGTCCGCCCTT-3'[SEQ ID NO:29];
signal 5:
5'-CCTGTCATGTGGACCACTTTGTACAAGAAAGCTGGGTTTCTATAGTGTCACCTAAATC-3' [SEQ ID NO:30] and

5'-GATTTAGGTGACACTATAGAAACCCAGCTTTCTTGTACAAAGTGGTCCACAT-3'[SEQ ID NO:31];
T7: 5'-TAATACGACTCACTATACCA-3'[SEQ ID NO:32];
T7-CyS primer: 5'-TAATACGACTCACTATA-3'[SEQ ID NO:33]; and
SP6 primer: 3'-AAGATATCACAGTGGATTTAG-5'[SEQ ID NO:34].
The library components (4 pmol each) were then mixed together and ligated using 100 U T4 DNA ligase (NEB) in 1X ligase buffer at 25 °C for 15 minutes. The ligase was then inactivated at 65 °C for 20 min.

Clean copy of the amended specification (paragraph on page 73 at lines 10-26)

Materials:

Oligonucleotides are selected which bind to the fragment chain and also serve as primers. Thus for example, for adjacent chains may be bound using for example the following primer pairs:

fragment chain 2 terminal (*with bound primer*):
5'TTCTATAGTGTCACCTAAATC3'[SEQ ID NO:35]
3'AAGATATCACAGTGGATTTAGCCTACCAGTACATCCAACGGCAACT5'[SEQ ID NO:36]

fragment chain 3 terminal (*with bound primer*):
5'GTCATGTAGGTTGCCGTTGATCCATCCTAATACGACTCACTATAGCA3'[SEQ ID NO:37]
3'ATTATGCTGAGTGATATCGT5'[SEQ ID NO:38]

The above exemplified primer regions are complementary and may thus be bound together.

Clean copy of the amended specification (paragraph on page 75 at lines 12-18)

Gene A has the following sequence at its first and last five bases (marked by underlining).

5'...GCTGGAGGCCTCCACTATGAAATCGCGTAGAG...[SEQ ID NO:80]
3'...CGACCTCCGGAGGTGATACTTTAGCGCATC.....[SEQ ID NO:98]

.....CTGGCGGAAAATGAGAAAATTCGACCTA...3'[SEQ ID NO:81]
...ACGACCGCCTTTTACTCTTTTAAGCTGG.....5'[SEQ ID NO:99]

Clean copy of the amended specification (paragraph on page 76 at line 1-page 77 at line 2)

Materials:

Initiation linker 1 (s):
5'ATT CGG TCG AGA TGC TCT CA3'[SEQ ID NO:39]

Initiator linker 1 (as):
5'CGA CTG AGA GCA TCT CGA CCG AAT3'[SEQ ID NO:40]

Initiation linker 2 (s):
5'GCG TTA CTG AGC GTA GCT CTG3'[SEQ ID NO:41]

Initiator linker 2 (as):
5'CTC TCA GAG CTA CGC TCA GTA ACG C3'[SEQ ID NO:42]

Propagation linker (s):
5'TGC TGC AGG AGC GAA TCT CNN NNN3'[SEQ ID NO:43]

Propagation linker (as):
5'GAG ATT CGC TCC TGC AGC A3'[SEQ ID NO:44]

Labeling linker 2 (s):
5'CTC TTG CTA TAG TGA GTC GTA TTA3'[SEQ ID NO:45]

Labeling linker 2 (as):
5'TAA TAC GAC TCA CTA TAG CA3'[SEQ ID NO:46]

Termination linker 1 (s):
5'AAG AGC TCA GGT CAT TGA CGT AGC TAT GAA3'[SEQ ID NO:47]

Termination linker 1/2 (as):
5'AGC TAC GTC AAT GAC CTG AG3'[SEQ ID NO:48]

Termination linker I (short version):
5'AAG AGA TGA A3'[SEQ ID NO:49]

Termination linker 2 (s):
5'ACC GCT CAG GTC ATT GAC GTA GCT TCA TT3'[SEQ ID NO:50]

Termination linker 2 (short version):
5'ACC GTC ATT3'

REMARKS

In response to a Notification of Missing Requirements under 35 U.S.C. §371 dated March 22, 2002 (a response copy is attached), an initial Sequence Listing is submitted, and its entry into the application is respectfully requested. Pursuant to 37 CFR § 1.821(e), an initial computer-readable form of the Sequence Listing is also submitted, and it is hereby certified